Pharmaceutica
Analytica Acta

Knaack, Pharmaceut Anal Acta 2012, 3:10
http://dx.doi.org/10.4172/2153-2435.1000e142

Editorial Open Access

The Importance of Analytical Chemistry in Quantitative Pharmaceutical Sciences

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The multidisciplinary study of pharmaceutical sciences involves techniques and knowledge derived from all fields of science including biology, mathematics, physics, toxicology, and chemistry with the goal of developing, understanding, and testing drugs. In the context of pharmaceutical sciences, analytical chemistry is the branch of science that provides knowledge of compound separation, identification and quantification that can be useful for measuring bioavailability of drugs, purifying drugs during synthesis, and identifying drug metabolic pathways. To accurately quantify drugs and metabolites in pharmacokinetic, transport, and delivery studies, a strong understanding of analytical chemistry principles is necessary and only well-characterized analytical methods should be used to ensure the integrity of collected data. This editorial will outline some key components of analytical analysis that are often overlooked when using quantitative methods for measuring drug and metabolite concentrations. While this short editorial is not comprehensive, it is intended to increase the awareness of the need for strong analytical chemistry skills in pharmaceutical research.

Quantitative methods used to measure the concentrations of target analytes in biological specimens should be thoroughly characterized for accuracy and limits of quantification. Method characterization requires the use of appropriate calibrators and quality control samples. These materials should be made in large batches and characterization should be performed for each batch and any time a new batch of materials is made. To create an effective calibration curve, calibrator materials should be of analytical-grade quality with known purities. When dissolving powdered materials, calibrated analytical balances should be used and corrections should be made to the resulting concentration for accuracy and precision of the balance as well as starting material purity. When diluting a stock solution, volumetric flasks should be used to obtain a high degree of accuracy. Calibration curves should then be analyzed over the course of at least seven runs spanning multiple days and the accuracy, precision, and coefficient of determination should be calculated for the specific batch of calibrators. For the lowest calibrator, accuracy should be within 30% and the coefficient of variation (CV) is usually within 20%. For most purposes, the lowest calibrator should also have a signal-to-noise ratio greater than ten. The coefficient of determination, r^2, should be >0.98 for analytical methods.

The choice of calibrator concentrations is extremely important and should not only focus on sensitivity at the low-concentration end of the calibration curve, but should also encompass reasonable concentrations that would be expected when analyzing unknown samples. Ideally, unknown samples containing analyte concentrations in the upper range of the calibration curve would not have to be diluted for accurate quantification. In cases where sample dilution is expected or necessary, the analytical method should be characterized using concentrated calibrators and quality control samples that are diluted prior to analysis. The accuracy of the resulting measurements should fall within an acceptable range relative to the calibration curve and undiluted quality control samples.

The purpose of quality control samples is to verify that the method is running correctly and to verify accuracy of the measurements. Quality control materials should be prepared alongside the calibrators at concentrations within the calibration curve. Ideally, at least two calibrators should reside above and below the highest and lowest quality controls, respectively. Furthermore, quality controls should approximate expected concentrations for unknown samples. Quality controls should be measured as unknowns against the calibration curve and the accuracy evaluated during each run. When the accuracy of quality controls falls out of predetermined acceptability criteria, usually within 20% accuracy, measurements of unknowns cannot be made using that calibration curve. In this scenario, the calibration curve should be reanalyzed and new calibrators made, if necessary.

When characterizing an analytical method, the limit of detection (LOD) and limit of quantification (LOQ) should be determined for each target analyte. The LOD corresponds to the lowest analyte concentration at which the signal-to-noise ratio is at least three, but can also be calculated using any one of several statistical methods. The LOQ represents the lowest concentration at which data can be quantified and is equal to the concentration of the lowest calibrator. Both the LOD and the LOQ should be determined from a minimum of seven analytical batches each containing at least five calibrators and a negative control. It is important to note that measured analyte concentrations falling below the LOQ and above the LOD should be presented as "below LOQ". Measured concentrations falling between the LOQ and LOD can have inaccuracies greater than 30% and so accurate concentrations cannot be provided. Similarly, samples in which no analyte is detected should be presented as "below LOD" indicating that there is a possibility that some analyte is present in the sample, but is at concentrations not detectable using the current method. Because calibrators and quality controls should be characterized for each batch of materials made, the LOD and LOQ should remain constant for each batch of materials. However, the LOD and LOQ can change when a new batch of materials is made and may be related to impurities in the starting material or inaccurate measurements made when creating the calibration curve. While the LOD and LOQ can be calculated and handled using a variety of methods, I have found that the above method provides the most honest and accurate way to convey data measured using analytical techniques.

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Received December 11, 2012; **Accepted** December 13, 2012; **Published** December 15, 2012

Citation: Knaack J (2012) The Importance of Analytical Chemistry in Quantitative Pharmaceutical Sciences. Pharmaceut Anal Acta 3: e142. doi:10.4172/2153-2435.1000e142

Analytical chemistry should play an important role in the measurement of drugs and metabolites in the field of pharmaceutical sciences. Scientists using analytical techniques to provide quantification of analytes should be familiar with methods for statistically analyzing collected data. The outlined suggestions in this editorial are only a basic guide for proper development of analytical methods and are based on experience with presentation of data regarding human exposure to various chemical toxins. Because accurate measurements of chemicals in biological specimens are critical for reporting disease states, determining pharmacokinetic parameters, and uncovering metabolic pathways, the highest degree of rigor should be placed on the methods used to collect this data.